

REMARKS

Reconsideration is requested.

Claim 1 has been revised, without prejudice, to define a method for treating a neurodegenerative ocular disease which includes diabetic retinopathy. New claim 41 defines a method for protecting photoreceptors. Support for the claims may be found throughout the specification. No new matter has been added.

Claims 30, 31, 33, 36 and 41 are pending.

The Section 112, first paragraph "enablement", rejection of claims 30, 31, 33 and 36 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following comments.

The Examiner's acknowledgment that the specification is enabling for the treatment of diabetic retinopathies is noted with appreciation. See page 2 of the Office Action dated December 28, 2009. The applicants submit that the claims are supported by an enabling disclosure and consideration of the following in this regard is requested.

The specification teaches one of ordinary skill how to make and use the claimed invention, for the use of etazolate for treating diabetic retinopathy, age related macular degeneration (ARMD) and retinitis pigmentosa. One of ordinary skill would not require undue experimentation to make and use the claimed invention.

ARMD is triggered by dysfunction in the retinal pigment epithelia, leading to the degeneration of macular photoreceptor cells. Oxidative stress and local inflammation play a major role in the pathologic processes of ARMD, as indicated e.g., in Beatty S et

al. (Surv Ophthalmol. 2000 Sep-Oct;45(2):115-34 "The role of oxidative stress in the pathogenesis of age-related macular degeneration." (Abstract attached)).

As a result, molecules demonstrating antioxidant, anti-inflammatory, and/or neuroprotective properties, are generally considered as novel therapeutic agents for ARMD (Hubschman JP et al, Clin Ophthalmol. 2009;3:167-74 "Age-related macular degeneration: current treatments" (copy attached)), and new therapeutics of ARMD can be inferred from models that allow transposition of results into the retinal context.

For example, an evaluated treatment for wet ARMD is an anti-VEGF therapy that derives from oncology, and a similar strategy has been followed with tubulin inhibitors such as Combretastatin.

It is known also that photoreceptor degeneration is accompanied by alterations in different aspects of the GABA system, which normally modulates the response to light stimulus from photoreceptors, as well as changes in the levels of cyclic nucleotides cAMP and cGMP which participates to the phototransduction cascade.

Therefore, acting on PDE4, PBR and the GABA(A) receptor is beneficial for the treatment of ARMD, modulating not only retinal neurons physiology.

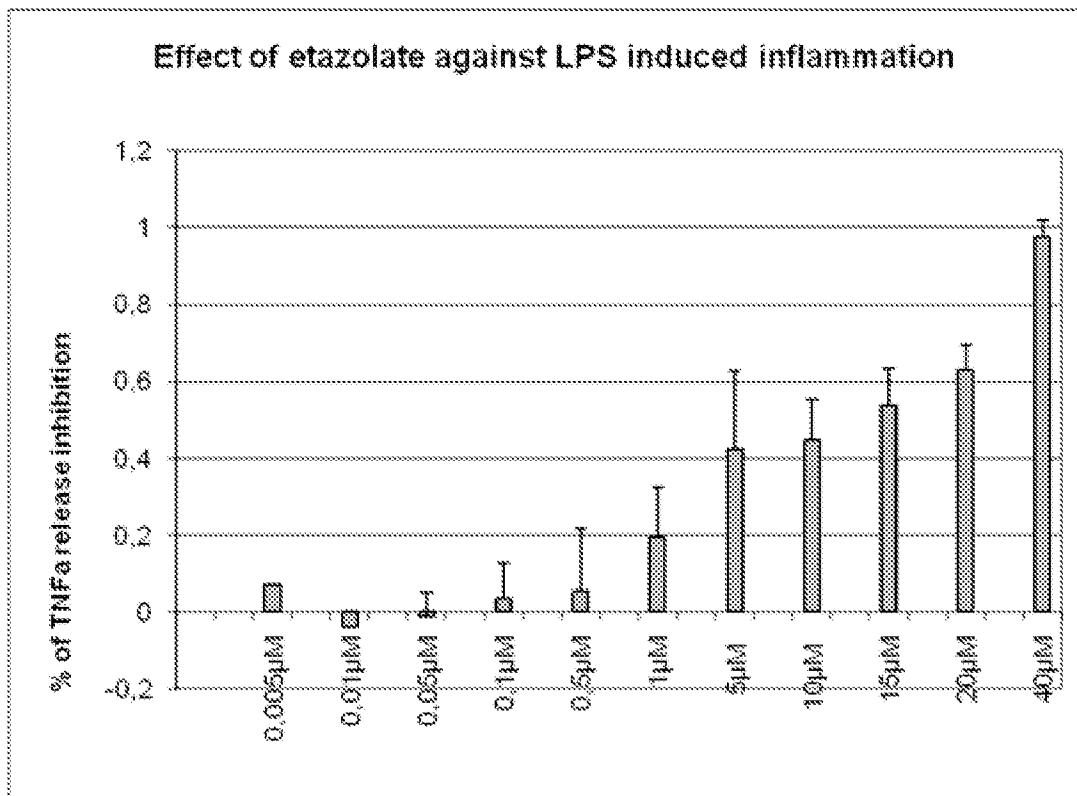
The present application demonstrates that etazolate shows neuroprotective activities against excitotoxic stresses for various neuronal types, as well as in the retinitis pigmentosa rd1 photoreceptor death model. In particular, the applicants have demonstrated, in examples 3-6, that:

- etazolate causes a 60% protective effect on cerebellar granular cells in the case of NMDA/serine treatment, and a 57% protective effect in the case of kainate-induced toxicity ;

- etazolate causes a substantial protective effect cortical neurons and ventral spinal cord cells ;
- etazolate is a PBR ligand which protects neurons from death during excitotoxic phenomena;
- the photoreceptors of rd1 mice treated with etazolate were better preserved than those of untreated rd-rd mice ;
- etazolate was well tolerated upon administration to human subjects and did not cause any side effects. Moreover, the plasma assays confirmed that absorption of the product in humans was good at high doses.

Furthermore, anti-inflammatory properties of etazolate have been duly documented by the applicants in the case of 6-hydroxidopamine-induced neuronal death (oxidative stress), beta-amyloid-induced stress (oxidative stress plus secondary excitotoxic stress: Marcade et al, J Neurochem. 2008 Jul;106(1):392-404 "Etazolate, a neuroprotective drug linking GABA(A) receptor pharmacology to amyloid precursor protein processing" (Abstract attached)) and LPS-induced neuroinflammation.

For the protective effect against LPS-induced toxicity, rat astrocytes were purified from newborn cortex and cultured for 7 days. Astrocytes were stimulated by LPS and the production of the pro-inflammatory cytokine TNF α was measured by ELISA in the culture supernatant (see histogram shown below). The data indicate a dose-dependent reduction of TNF α production by etazolate, indicative of an anti-inflammatory activity of etazolate.



Taken together, these results provide clear, credible, specific and substantial in vitro and in vivo data to establish the utility of etazolate in the treatment of ARMD and other retinal degenerations such as retinitis pigmentosa where photoreceptor cell death appears to be governed by similar pathologic mechanisms such as changes in cyclic nucleotide metabolism and oxidative and excitotoxic stresses as well as pro-inflammatory mechanisms. It is therefore submitted that the claims, which relate to the use of a specific compound for treating specified, mechanistically-related diseases, are supported by an enabling disclosure.

Withdrawal of the Section 112, first paragraph “enablement”, rejection is requested.

The Section 102 rejection of claims 30, 31 and 36 over Fung (U.S. Patent No. 6,326,201), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing remarks.

The Examiner’s indication that claim 33 “appears to be free of the prior art” (see page 7 of the Office Action dated December 28, 2009) is noted, with appreciation.

The Examiner contends, however, that a method of treating diabetic retinopathies using etazolate would have been obvious in view of Fung which, allegedly, would teach that the decrease in cAMP is linked to pancreatic performance in diabetic patients. Applicants respectfully disagree and consideration of the following is requested.

Fung relates to the use of cAMP-elevating agents to repair/stimulate pancreatic function in diabetic subjects via ex vivo/in vivo pancreatic progenitor cells recruitment.

As indicated, Fung proposes to use cyclic AMP (cAMP) agonists to induce differentiation of pancreatic progenitors into cells of endocrine or exocrine phenotype to regenerate pancreas. Furthermore, while etazolate is cited among a list of potential cAMP agonists, there is no description of any result or activity of this compound.

The present invention is based on the unexpected findings that etazolate can directly protect retinal integrity via neuroprotective mechanisms. This is distinct and remote from and not suggested by the teaching of Fung.

SCHWEIGHOFFER et al.
Appl. No. 10/541,503
Atty. Ref.: 3665-152
Amendment
Monday, March 29, 2010

Current treatments of diabetic retinopathy are laser photocoagulation and vitrectomy. Insulin control is not sufficient to control this pathology. Furthermore, type 2 diabetes patients treated with rosiglitazone are at higher risk for problems with leaks at the level of the macula. Therefore, repairing pancreatic function by PDE inhibition in order to protect the retina is not scientifically founded and the ordinarily skilled person would not have found any motivation or teaching in Fung to arrive at the instantly claimed invention.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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